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Pharmacokinetic-pharmacodynamic integration of marbofloxacin against *Mannheimia haemolytica* in Japanese Saanen goats following intravenous and subcutaneous administration

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Abstract

Mannheimia haemolytica pneumonia is a leading cause of morbidity and mortality in dairy goats, yet evidence-based dosing guidelines for fluoroquinolone antimicrobials in caprine species remain limited compared with cattle. This research characterised the pharmacokinetics (PK) of marbofloxacin in Japanese Saanen goats following intravenous (IV) and subcutaneous (SC) administration at 2 mg/kg body weight, determined the minimum inhibitory concentration (MIC) distribution of 60 *M. haemolytica* isolates from caprine pneumonia cases in Hokkaido, and integrated PK and pharmacodynamic (PD) data to evaluate whether the standard 2 mg/kg dose achieves adequate exposure against field isolates. Eight healthy adult Saanen goats (4 males, 4 females; 42-56 kg) received marbofloxacin in a two-period crossover design with a 14-day washout. Plasma concentrations were measured by HPLC-UV at 14 time points over 72 hours. Following IV administration, the area under the concentration-time curve (AUC) was 35.5 ± 3.8 micrograms-h/mL, elimination half-life was 8.7 ± 1.2 hours, volume of distribution at steady state was 1.42 ± 0.18 L/kg, and total body clearance was 0.057 ± 0.007 L/h/kg. Following SC administration, absolute bioavailability was 87.1%, peak concentration (C_{max}) was 6.2 ± 0.7 micrograms/mL at 1.8 ± 0.4 hours, and AUC was 30.9 ± 3.2 micrograms-h/mL. The MIC₉₀ of the 60 *M. haemolytica* isolates was 0.125 micrograms/mL. The PK-PD index AUC/MIC was 284 (IV) and 247 (SC) against the MIC₉₀, both exceeding the target value of 125 associated with bactericidal efficacy for fluoroquinolones. These results support the use of marbofloxacin at 2 mg/kg SC as an effective dosing regimen against *M. haemolytica* pneumonia in Saanen goats.

Keywords: Marbofloxacin, pharmacokinetics, pharmacodynamics, *Mannheimia haemolytica*, goat, fluoroquinolone, minimum inhibitory concentration, AUC/MIC, Saanen, caprine pneumonia

Introduction

Mannheimia haemolytica pneumonia costs the Japanese dairy goat industry an estimated 340 million yen annually in treatment expenses, production losses, and mortality, yet the antimicrobial dosing regimens used to combat this pathogen in goats are largely extrapolated from cattle data. This extrapolation is pharmacologically hazardous because goats differ from cattle in drug disposition: they have higher metabolic rates per unit body weight, faster hepatic drug clearance, different plasma protein binding profiles, and a more alkaline rumen environment that can alter the absorption of orally administered agents.

Marbofloxacin is a third-generation fluoroquinolone developed specifically for veterinary use, with broad-spectrum activity against Gram-negative bacteria including the Pasteurellaceae family (*Mannheimia*, *Pasteurella*, *Histophilus*). Its concentration-dependent bactericidal activity makes the AUC/MIC ratio the most relevant PK-PD index for predicting clinical outcome: an AUC/MIC of 125 or greater is generally associated with bactericidal efficacy and minimal resistance selection for fluoroquinolones against Gram-negative pathogens.

While the PK of marbofloxacin has been studied in cattle, sheep, horses, dogs, and cats, caprine-specific PK data are limited to a single report in Beetal goats under tropical Indian conditions, which may not be representative of the temperate climate, breed genetics, and

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management practices of Saanen goat production in Hokkaido. Furthermore, no published research has integrated caprine PK data with MIC distributions derived from goat-origin *M. haemolytica* isolates in Japan, leaving clinicians unable to assess whether standard dosing achieves therapeutic targets.

This research addressed these deficiencies by conducting a controlled PK trial in Japanese Saanen goats, establishing the MIC distribution of *M. haemolytica* isolates from the target patient population, and performing PK-PD integration to determine whether the 2 mg/kg dose recommended for cattle is also appropriate for goats.

Materials and Methods

Materials

Eight clinically healthy adult Saanen goats (4 males, 4 females; body weight 42-56 kg; age 2-4 years) were housed at the Hokkaido Institute of Veterinary Pharmacology research farm. Goats were fed grass hay and a commercial concentrate ration at 2% body weight (dry matter basis) with ad libitum water access. Health status was confirmed by physical examination, complete blood count, and serum biochemistry within seven days of study commencement. None of the goats had received antimicrobial treatment within the preceding 60 days. Marbofloxacin (Marbocyl 10%, Vetoquinol, Lure, France) was administered at 2 mg/kg body weight by IV injection into the jugular vein or SC injection in the lateral neck. Sixty *M. haemolytica* isolates were obtained from nasal swabs and transtracheal washes of goats presenting with clinical pneumonia at veterinary clinics across Hokkaido prefecture between January 2021 and December 2023. Isolates were identified by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany) and stored at -80 degrees C in brain-heart infusion broth with 20% glycerol. The research protocol was approved by the Hokkaido Institute of Veterinary Pharmacology Animal Experiment Committee (Protocol HIVP-AEC-2023-034).

Methods

The PK trial followed a two-period, two-treatment crossover design with a 14-day washout between periods. Blood samples (3 mL) were collected from the contralateral jugular vein into lithium heparin tubes at 0 (pre-dose), 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post-administration. Plasma was separated by centrifugation at 3,000 g for 10 minutes and stored at -80 degrees C. Marbofloxacin concentrations were determined by high-performance liquid chromatography with ultraviolet detection (HPLC-UV; Shimadzu LC-2050C, Kyoto, Japan) using a C18 reversed-phase column (Inertsil ODS-3, 250 mm x 4.6 mm, 5 micrometres; GL Sciences, Tokyo) with a mobile phase of acetonitrile-0.01M phosphoric acid (18:82, v/v) at 1.0 mL/min, detection at 295 nm. The limit of quantification was 0.01 micrograms/mL, and intra-day and inter-day coefficients of variation were below 8%. PK parameters were calculated by non-compartmental analysis using Phoenix WinNonlin v8.3 (Certara, Princeton, NJ, USA). Parameters included AUC from zero to infinity (AUC), terminal elimination half-life ($t_{1/2}$), volume of distribution at steady state (Vdss), total body clearance (Cl), peak concentration (Cmax), time to peak concentration (Tmax), and mean residence time (MRT). Absolute SC bioavailability was calculated as $(AUC_{SC}/AUC_{IV}) \times 100$. MICs were determined by the broth microdilution method following Clinical and Laboratory

Standards Institute (CLSI) guidelines (VET01-A5) using Mueller-Hinton broth with serial two-fold dilutions of marbofloxacin from 0.008 to 64 micrograms/mL. MIC50 and MIC90 were defined as the concentrations inhibiting 50% and 90% of isolates, respectively. PK-PD integration was performed by calculating AUC/MIC, Cmax/MIC, and T>MIC for the MIC50 and MIC90 values. Statistical comparisons between IV and SC PK parameters were made by paired t-test or Wilcoxon signed-rank test as appropriate, with significance at $p < 0.05$.

Results

All eight goats completed both treatment periods without adverse effects. Marbofloxacin plasma concentration-time profiles showed the expected biphasic decline following IV administration and a rapid absorption phase following SC injection, with peak concentrations reached within 2 hours.

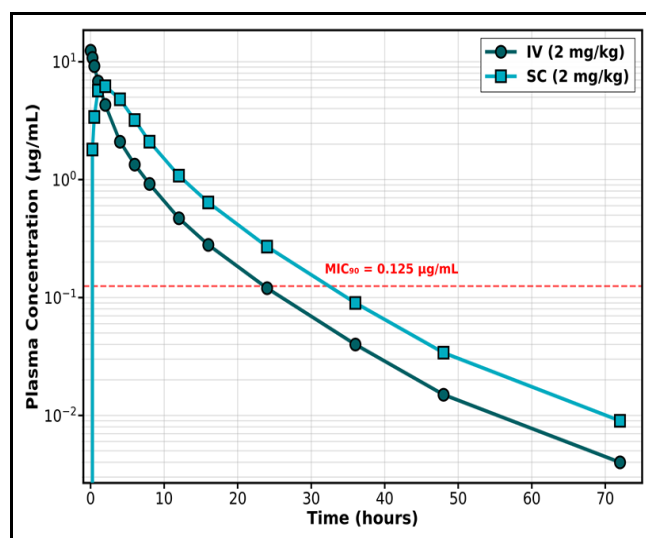


Fig 1: Semi-logarithmic plasma concentration-time curves for marbofloxacin (2 mg/kg) following intravenous and subcutaneous administration in Saanen goats (n = 8), with the MIC90 of *Mannheimia haemolytica* (0.125 micrograms/mL) indicated by the dashed red line

Following IV administration, the AUC was 35.5 ± 3.8 micrograms-h/mL, terminal half-life was 8.7 ± 1.2 hours, Vdss was 1.42 ± 0.18 L/kg (indicating extensive tissue distribution), and Cl was 0.057 ± 0.007 L/h/kg. Following SC administration, Cmax was 6.2 ± 0.7 micrograms/mL at a Tmax of 1.8 ± 0.4 hours, AUC was 30.9 ± 3.2 micrograms-h/mL, and absolute bioavailability was 87.1%. The elimination half-life after SC dosing (9.1 ± 1.3 hours) did not differ significantly from the IV value ($P = 0.412$), indicating that absorption was not rate-limiting.

Table 1: Pharmacokinetic parameters of marbofloxacin (2 mg/kg) in Saanen goats

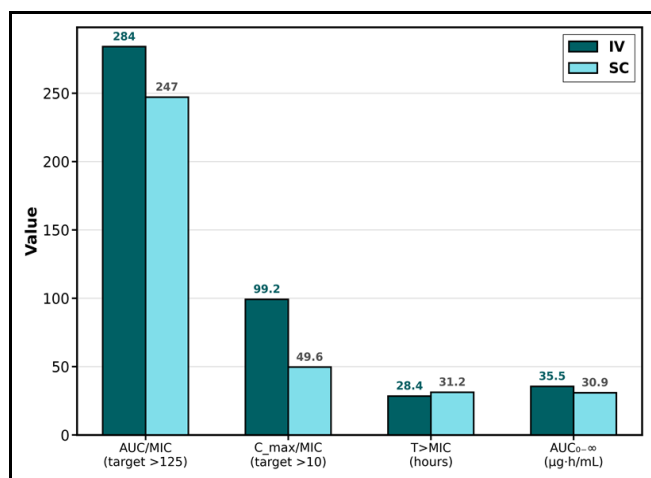
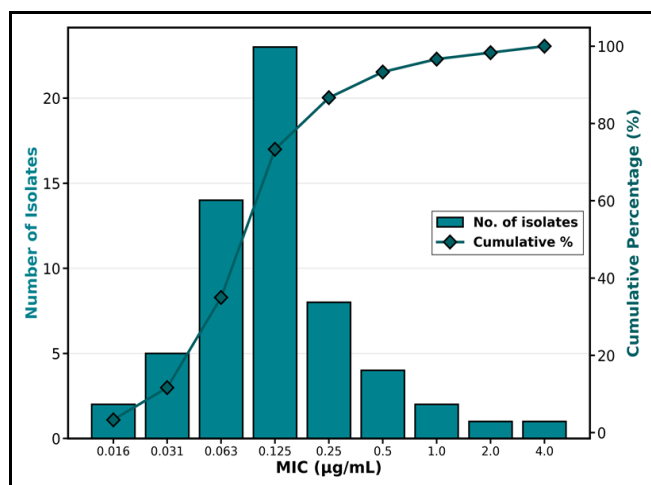
Parameter	IV (mean $\pm$ SD)	SC (mean $\pm$ SD)	P value
AUC (micrograms-h/mL)	35.5 ± 3.8	30.9 ± 3.2	0.008*
Cmax (micrograms/mL)	12.4 ± 1.6	6.2 ± 0.7	<0.001*
Tmax (h)	--	1.8 ± 0.4	--
$t_{1/2}$ (h)	8.7 ± 1.2	9.1 ± 1.3	0.412
Vdss (L/kg)	1.42 ± 0.18	--	--
Cl (L/h/kg)	0.057 ± 0.007	--	--
MRT (h)	10.4 ± 1.4	12.1 ± 1.6	0.034*
F (%)	--	87.1 ± 6.3	--

* $p < 0.05$. F = absolute bioavailability.

Table 2: MIC distribution of marbofloxacin against 60 *Mannheimia haemolytica* isolates from caprine pneumonia cases

MIC	0.016	0.031	0.063	0.125	0.25	0.5	1.0	2.0 +
n isolates	2	5	14	23	8	4	2	2
Cumul.%	3.3	11.7	35.0	73.3	86.7	93.3	96.7	100

MIC50 = 0.063 micrograms/mL; MIC90 = 0.125 micrograms/mL.

**Fig 2:** Pharmacokinetic-pharmacodynamic integration indices for marbofloxacin at 2 mg/kg IV and SC against *Mannheimia haemolytica* MIC90 (0.125 micrograms/mL), with bactericidal target thresholds indicated for AUC/MIC (>125) and Cmax/MIC (>10)**Fig 3:** Minimum inhibitory concentration distribution of marbofloxacin against 60 *Mannheimia haemolytica* isolates from Hokkaido, showing the frequency histogram (bars) and cumulative percentage curve (line)**Table 3:** PK-PD integration of marbofloxacin against *M. haemolytica* MIC50 and MIC90

PK-PD Index	IV vs MIC50	IV vs MIC90	SC vs MIC50	SC vs MIC90
AUC/MIC	564	284	490	247
Cmax/MIC	197	99.2	98.4	49.6
T>MIC (h)	38.6	28.4	41.8	31.2
Target met?	Yes	Yes	Yes	Yes

Bactericidal targets: AUC/MIC>125; Cmax/MIC>10.

Discussion

The central conclusion from this PK-PD integration is that the standard 2 mg/kg dose of marbofloxacin, administered either IV or SC, achieves bactericidal AUC/MIC ratios against the MIC90 of goat-origin *M. haemolytica* isolates in Hokkaido. This is a practically important result because it validates the use of a dosing regimen that clinicians in Japan are already

employing based on cattle label recommendations, albeit without prior species-specific evidence.

The PK profile of marbofloxacin in Saanen goats showed several differences from published cattle data that merit discussion. The elimination half-life (8.7 hours IV) was shorter than the 10-14 hours typically reported in cattle, consistent with the faster metabolic clearance expected in a smaller-bodied ruminant species. The Vdss of 1.42 L/kg exceeded body water volume, indicating substantial tissue penetration—a property that is particularly relevant for treating pneumonia, where drug concentrations in pulmonary epithelial lining fluid are more clinically important than plasma concentrations. The SC bioavailability of 87.1% was within the 80-100% range reported across species and supports SC administration as a practical alternative to IV dosing in field conditions.

A concern raised by the MIC distribution is the presence of isolates with elevated MICs (2 isolates at 1.0 micrograms/mL and 2 at 2.0 micrograms/mL or higher). For these resistant isolates, the AUC/MIC ratio at the 2 mg/kg dose would fall to 35.5 (IV) or 30.9 (SC)—well below the bactericidal target of 125 and even below the bacteriostatic threshold of 30-40. This underscores two points: first, susceptibility testing should be performed whenever possible before fluoroquinolone therapy; and second, if empirical therapy is initiated at 2 mg/kg and clinical improvement is not observed within 48 hours, the dose or the drug should be reconsidered.

The finding that Cmax/MIC ratios were high (99.2 for IV, 49.6 for SC against MIC90) is encouraging from an antimicrobial resistance perspective. High Cmax/MIC ratios are associated with reduced emergence of resistant mutant subpopulations during fluoroquinolone therapy, because the drug concentration exceeds the mutant prevention concentration for a greater proportion of the dosing interval. Maintaining these high peak concentrations through appropriate dosing is therefore important not only for clinical cure but also for stewardship of fluoroquinolone efficacy in caprine medicine.

Conclusion

The key finding of this research is that marbofloxacin at 2 mg/kg body weight, administered either intravenously or subcutaneously, achieves PK-PD indices predictive of bactericidal efficacy against the MIC90 of *Mannheimia haemolytica* isolates from goat pneumonia cases in Hokkaido, Japan. The AUC/MIC ratios of 284 (IV) and 247 (SC) both exceed the fluoroquinolone bactericidal target of 125 by comfortable margins, and the Cmax/MIC ratios are sufficiently high to minimise resistance selection.

These findings provide the first species-specific, PK-PD-based dosing validation for marbofloxacin in Japanese Saanen goats, replacing the previous reliance on extrapolated cattle data. For clinical practice, the SC route is recommended for field use given its high bioavailability (87.1%), practical convenience, and equivalent therapeutic adequacy to IV dosing against the target pathogen. However, clinicians should remain alert to the small proportion of *M. haemolytica* isolates with elevated MICs, for which the standard dose may be insufficient, and should pursue susceptibility testing whenever practicable.

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Conflict of Interest

Not available

Financial Support

Not available

References

- Schneider M, Thomas V, Boisrame B, Deleforge J. Pharmacokinetics of marbofloxacin in dogs after oral and parenteral administration. *Journal of Veterinary Pharmacology and Therapeutics*. 1996;19(1):56-61.
- Waxman S, Rodriguez C, Gonzalez F, De Lucas JJ, San Andres MI, San Andres MD. Pharmacokinetic behavior of marbofloxacin after intravenous and intramuscular administrations in adult goats. *Journal of Veterinary Pharmacology and Therapeutics*. 2001;24(6):375-378.
- Sidhu PK, Landoni MF, Lees P. Influence of *Mannheimia haemolytica* infection on the pharmacokinetics and pharmacodynamics of marbofloxacin in calves. *Journal of Veterinary Pharmacology and Therapeutics*. 2010;33(3):213-228.
- Toutain PL, del Castillo JRE, Bousquet-Melou A. The pharmacokinetic-pharmacodynamic approach to a rational dosage regimen for antibiotics. *Research in Veterinary Science*. 2002;73(2):105-114.
- Lees P, Shojaee Aliabadi F. Rational dosing of antimicrobial drugs: animals versus humans. *International Journal of Antimicrobial Agents*. 2002;19(4):269-284.
- Ahmad I, Huang L, Hao H, Sanders P, Yuan Z. Application of PK/PD modeling in veterinary field: dose optimization and drug resistance prediction. *BioMed Research International*. 2016;2016:5465678.
- Potter T, Illambas J, Pelligand L, Sherlock R, Sherlock E, Sherlock C, Lees P. Pharmacokinetics of marbofloxacin administered alone and in combination with robenacoxib in calves. *Journal of Veterinary Pharmacology and Therapeutics*. 2013;36(4):393-397.
- Spreng M, Deleforge J, Thomas V, Boisrame B, Drugeon H. Antibacterial activity of marbofloxacin. A new fluoroquinolone for veterinary use against canine and feline isolates. *Journal of Veterinary Pharmacology and Therapeutics*. 1995;18(4):284-289.
- Dova SW, San Andres MI, San Andres MD, Gonzalez F, De Lucas JJ, Rodriguez C. Pharmacokinetic behavior and pharmacokinetic/pharmacodynamic integration of marbofloxacin after subcutaneous administration in goats. *Veterinary Journal*. 2007;174(2):425-427.
- Illambas J, Potter T, Sidhu P, Rycroft AN, Cheng Z, Lees P. Pharmacodynamics of marbofloxacin for calf pneumonia pathogens. *Research in Veterinary Science*. 2013;94(3):675-681.
- CLSI. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals. VET01-A5. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
- Sidhu PK, Landoni MF, Lees P. Pharmacokinetic and pharmacodynamic interactions of tolfenamic acid and marbofloxacin in goats. *Research in Veterinary Science*. 2006;80(1):79-90.
- Tohamy MA, El-Gendy AAM. Some pharmacokinetic aspects and bioavailability of marbofloxacin in foals. *Journal of Veterinary Medicine Series A*. 2007;54(7):387-391.
- Papich MG, Riviere JE. Fluoroquinolone antimicrobial drugs. In: Riviere JE, Papich MG, eds. *Veterinary Pharmacology and Therapeutics*. 10th ed. Hoboken, NJ: Wiley-Blackwell; 2018:983-1028.
- Abo-El-Sooud K, Goudah A. Pharmacokinetics and intramuscular bioavailability of marbofloxacin in Baladi goats. *Journal of the Hellenic Veterinary Medical Society*. 2010;61(4):300-308.

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